Dopamine Receptors and Their Behavioral Correlates
Pharmacology Biochemistry & Behavior, Vol. 17, Suppl. 1,pp. 11-19, 1982. Printed in the U.S.A.

Structure Activity Relationships of Presynaptic Dopamine Receptor Agonists[1]

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BHATNAGAR, R. K., S. P. ARNERIĆ, J. G. CANNON, J. FLYNN AND J. P. LONG. *Structure activity relationships of presynaptic dopamine receptor agonists*. PHARMAC. BIOCHEM. BEHAV. 17: Suppl. 1,11-19, 1982.—Structure activity relationship (SAR) studies have identified many structural entities that interact with dopamine receptors. The aminotetralin structure may be regarded as an active moiety of apomorphine. An unanswered question concerns the SAR of the 4,7-dimethoxy indane derivatives. These agents do not appear to match well with models of dopamine receptors. At least there can be little doubt that SAR research has been a powerful stimulus during the past decade for understanding the function, distribution, and spatial aspects of dopamine receptors.

Structural activity relationship   Presynaptic dopamine receptor agonists

POSSIBLE involvement of dopamine and dopamine receptors in neuronal function was supported by the work of Ehringer and co-workers more than 20 years ago. They demonstrated decreased dopamine in the caudate nucleus at autopsy of patients with Parkinson's disease [5]. This knowledge led to the introduction of L-dopa into therapy for Parkinson patients. Ernst demonstrated that apomorphine induced gnawing behavior in rats by interacting with dopamine receptors [6]. This important observation served as a stimulus for those interested in structure activity relationships (SARs) of agents interacting with dopamine receptors. What portion of the apomorphine molecule was necessary? The structural relationships of apomorphine, dopamine, and aminotetralins are shown in Fig. 1.

The possible spatial orientation of dopamine (α-β-conformer) for optimal biological activity can be evaluated using rigid ring systems. It has been noted that isoapomorphine, which corresponded to the β-conformer of dopamine, was much less active than apomorphine. However, in the aminotetralin series the two di-hydroxy isomers, M-7 and TL-99 were approximately equal in activity as inhibitors of the adrenergic nerve terminal. The unexpected high activity of both aminotetralins in comparison with the divergent activity found for apomorphine versus isoapomorphine suggested that chemical factors other than spatial relations to dopamine were important. Similar divergent activity was found for benzo [f] quinolines versus benzo [g] quinolines; this will be discussed later.

Questions concerning types of receptors that would be inhibitors at nerve terminals were also raised concerning apomorphine, dopamine, and aminotetralins. In the cat, both M-7 and TL-99 were antagonized by haloperidol and not antagonized by phentolamine. In the dog, both phentolamine and haloperidol were effective antagonists of both compounds. These findings indicated species differences and apparent differences in receptor interactions that could be introduced by minor alterations in structure.

QUESTIONS CONCERNING SAR STUDIES—BIOLOGY

Any valid SAR study must meet several experimental criteria. Some of the factors that should be considered are outlined as follows:

1. Different Receptor Types at Presynaptic and Postsynaptic Sites

Several examples of close structural analogs interacting with dopamine and/or α-receptors have been reported. These differences are suggested by using different antagonists as well as various radioligands in *in vitro* assays.

2. Species Differences or Organ Specificity Within a Species

Wide variation in reactivity among species is observed when comparing clonidine and apomorphine (Fig. 2). Work with rats and guinea pigs has yet to demonstrate presynaptic dopamine receptors on adrenergic nerve terminals innervating atria. However, dopamine receptors producing inhibition of adrenergic nerves innervating the central ear artery of rabbits have been demonstrated [25]. Thus, there may be

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[1] This work was supported in part by NIH grants GM-22365, NS-12121 and a grant from Eli Lilly and Company.

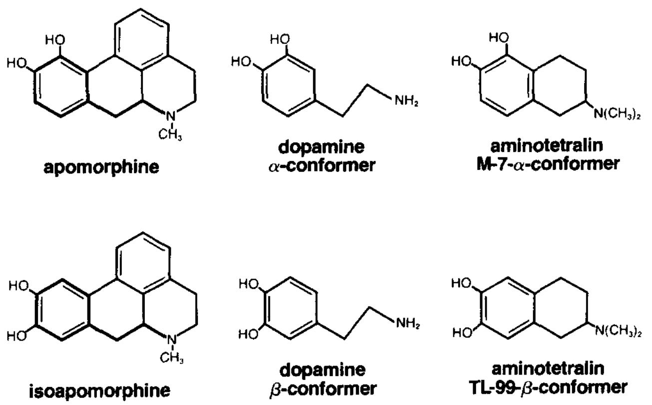


FIG. 1. The relationship of the isomers of apomorphine and aminotetralins to the two possible α- and β-conformers of dopamine.

considerable variation in distribution of presynaptic dopamine receptors within species.

3. Central versus Peripheral Presynaptic Dopamine Receptors

Also to be considered are the potential differences between presynaptic dopamine receptors within the central nervous system versus presynaptic dopamine receptors of the peripheral nervous system. Reactivity of dopamine receptors differs following chronic haloperidol administration. Central presynaptic dopamine receptors associated with inhibition of locomotor activity are supersensitive to apomorphine following chronic haloperidol treatment; the supersensitivity is antagonized by lithium [28], whereas peripheral dopamine receptors on the adrenergic nerve terminal appear to become subsensitive [29].

4. Quantification of Presynaptic Dopamine Receptor Activity

Of prime concern for those interested in SARs is how to quantify presynaptic dopamine receptor activity. For adrenergic neuronal transmission in the peripheral nervous system a number of preparations have been used *in vivo*, for example, nictitating membrane [13]; cardioaccelerator nerves [16]; and adrenergic transmission to the hind limb [15]. Some of the *in vitro* preparations are atria of cats [12]; central ear artery of rabbits [25]; and dog veins [11].

Perhaps the best defined area of the central nervous system (CNS) involves the caudate nucleus and even it is most complex. As is indicated below we must consider not only presynaptic autoreceptors and postsynaptic-induced negative feedback inhibition, but also other types of neuronal activity that may modify dopaminergic neuronal transmission in either a positive or negative manner. These interrelationships are shown in Fig. 3. See Moore and Wuerthele [20] for further discussion.

Experimental methods for evaluating presynaptic dopamine receptor activity involving the caudate nucleus include electrophysiological recordings [1,24] studies of dopa levels [4,30], and binding studies using various radioligands [27]. There is considerable agreement that inhibition of locomotion in mice or rats is an index of presynaptic activity involving the limbic system [3,26]. Many of the known dopamine analogs which are believed to be presynaptic dopamine receptor agonists are extremely active in this behavioral test. The interpretation and importance of binding studies reported in this article for spiroperidol and ADTN using calf caudate are confounded by low sensitivity (μM range instead of nM range). For comparison the IC_{50} of *d*-butaclamol for ^3H-spiroperidol binding was 75 nM. The IC_{50} values may reflect non-specific effects due to differences in lipophilicity and free energy binding. These values, however, do indicate the relative effects on binding of dopamine analogs in SAR studies and correlate well with *in vivo* experiments reported in this article. Alternately, the compounds may interact with other receptors such as α_1, α_2, 5-HT, and β-receptors.

	in vivo		in vitro		
	Cardioaccelerator nerve ED_{50} μg/kg		Field Stimulation ED_{50} μM		
	dog	cat	rat	guinea pig	cat
Apomorphine	25	20	>>40	>>40	0.07
Clonidine	15	>>100[1]	1.0	0.08	0.06

[1] A complete dose-response curve for inhibition with clonidine in cats using *in vivo* experiments cannot be obtained.
Clonidine appears to be much more effective using *in vitro* cat atria and complete dose response curves are obtained.

FIG. 2. Comparisons of the effectiveness of apomorphine and clonidine for inhibiting sympathetic neuronal stimulation using *in vivo* and *in vitro* experiments. A frequency of 2 Hz was used in all experiments. [1]A complete dose-response curve for inhibition with clonidine in cats using *in vivo* experiments cannot be obtained. Clonidine appears to be much more effective using *in vitro* cat atria; complete dose-response curves are obtained.

SAR STUDIES—CHEMISTRY

1. Dopamine and Derivatives

Research with phenylalkyl derivatives has produced compounds with a wide divergence of activity. Prototypes are shown in Fig. 4. The interaction of dopamine with presynaptic receptors on the adrenergic neuron is unique in that the presence of an amine uptake inhibitor such as cocaine is required to produce inhibition of transmission [13,14]. There have been no reports of amine uptake inhibitors modifying the activity of other dopamine receptor agonists. N-*di*-alkyl substitutions of dopamine or derivatives of the 3-monohydroxy analog of dopamine produce adrenergic inhibitory agents. The presence of cocaine does not modify the potency of these agents. The 3-monohydroxy derivative has a duration of action much longer than the catechol derivatives [7]. An excellent example of apparent inversion of receptor type is seen when comparing the N-*di*-CH_3 and N-*di*-C_2H_5 derivatives of dopamine. Various receptor blocking agents indicate that α_2-receptors are involved in neuronal inhibition with the N-*di*-CH_3 derivative and dopamine receptors are involved with the N-*di*-C_2H_5 agent. This apparent inversion of receptor mechanisms occurs with other series of compounds. The presynaptic activity of the N-*di*-*n*-propyl derivative is similar to that of the N-*di*-ethyl derivative. In this series as well as other series N-*di*-*n*-butyl substitution is most unfavorable for activity.

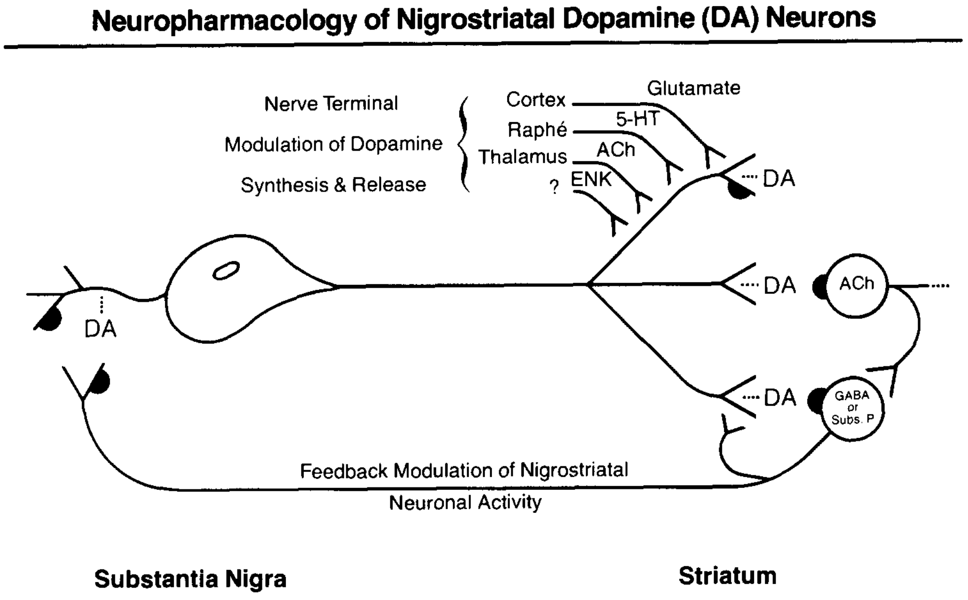


FIG. 3. Various mechanisms capable of modifying presynaptic dopaminergic function in the nigrostriatal pathway.

Propyl-butyl derivatives are active [8]. The duration of action for N-*di*-alkyl derivatives of dopamine is less than 5 minutes. Inhibition of neuronal transmission can be maintained by intravenous infusion. Branching of the alkyl chain of dopamine at the α-carbon yields inactive compounds, which would not be expected since there is branching of the carbon adjacent to the nitrogen in aminotetralin [5].

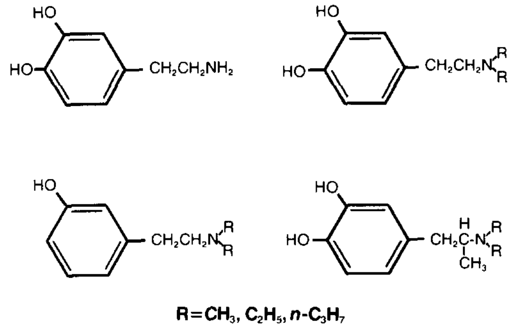


FIG. 4. Analogs of dopamine that modify neuronal activity.

2. *Derivatives of Aminotetralin*

The first attempt to determine the active moiety of apomorphine involved phenanthrene derivatives, which were inactive. It was later determined that derivatives of aminotetralin and indane were very active compounds [2,19]. These structures can now be regarded as active moieties of apomorphine. Some of the biological properties of aminotetralin derivatives are summarized in Table 1. Derivatives of indane will be discussed later.

Several structural features of aminotetralin derivatives should be noted. The *di*-OH in the 5,6; 6,7; or 5,7 positions are potent neuronal inhibiting agents. The 5,8-*di*-OH derivatives were found to be inactive. Perhaps these compounds are unstable derivatives. With mono-OH substitution [18] in the 5 or 6 positions, very active presynaptic inhibitors of adrenergic transmission are obtained. The 7-OH derivative is less active. With the 5,6 or 6,7-*di*-OH derivatives of aminotetralins, the primary amines are less potent than the tertiary amines with *di*-alkyl substitution. It should be noted that the 6,7-*di*-OH derivative (ADTN) is nearly as active as dopamine for inducing dilatation of the renal vascular bed [9]. The 5,6-*di*-OH derivative is nearly inactive as a renal artery vasodilator.

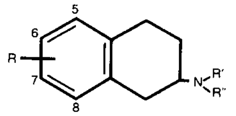
The 2-N-*mono*-CH_3 and 2-N-*mono*-i-C_3H_7 derivatives of 5,6-*di*-OH aminotetralin are potent β_2-receptor agonists. Unfortunately, the agents are not effective orally. The 6,7-*di*-OH aminotetralin derivatives are nearly inactive as β_2-receptor agonists. Do these studies indicate that epinephrine and isoproterenol interact with β-receptors as the α-conformer and not the β-conformer?

Biological activity observed for methoxy substitutions on the phenyl ring of aminotetralin derivatives is determined by both the ring position of methoxy substitution and also by N-alkyl substitution (Table 2). The 5,8-*di*-methoxy derivatives with N-substitution from H to *di*-CH_3 are potent, long-acting α_1-receptor agonists [23]. This property is not surprising since these compounds are cyclic analogs of methoxamine. Antagonism of apomorphine-induced gnawing in rats and emesis in dogs are also observed [21]. Thus, these agents are α_1-receptor agonists and are capable of inhibiting dopamine receptors at some sites. The N-*di*-*n*-propyl analog of the methoxy derivative is a potent, long-acting (>1.0 hr) inhibitor of peripheral adrenergic neuronal transmission. This compound appears to exhibit minimal involvement of dopaminergic function within the CNS.

A new biological finding for the aminotetralin derivatives is a compound which is substituted with 6,7-*di*-OCH_3 and N-*di*-*n*-C_3H_7 (TL-1000). This compound inhibits vagal nerve

TABLE 1

SOME HYDROXY DERIVATIVES OF AMINOTETRALIN



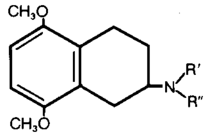
Derivative	R=*di*-OH	R′	R″	CAN-ED_{50}* μM/kg	Calf Caudate *in vitro* binding IC_{50} nM Spiroperidol	ADTN	Rat Rotation APO=1	Dog Emesis APO=1
JOD 173	5,6	H	H	↑HR			Inactive	
M-8	5,6	H	CH_3	—			Weak	0.39
M-7	5,6	CH_3	CH_3	0.0049	20,000		0.08	2.57
TL-259	5,6	C_2H_5	C_2H_5				NT	6.1
TL-102	5,6	C_3H_7	C_3H_7	0.0082			0.99	4.75
ADTN	6,7	H	H	0.01		200	NT	0.047
TL-218	6,7	H	CH_3	0.001			NT	0.187
TL-99	6,7	CH_3	CH_3	0.0004			0.01	0.584
TL-196	6,7	H	C_3H_7	0.0061			NT	0.245
TL-232	6,7	C_3H_7	C_3H_7	0.0024			0.32	1.54
AB-118	5,7	H	H	↑HR	180,000	51,000	NT	Inactive†
AB-40	5,7	H	C_3H_3	↑HR	110,000	250,000	NT	Inactive†
AB-82	5,7	C_3H_7	C_3H_7	0.021	177,000		NT	NT
AB-88	5,7	H	C_2H_5	0.04	130,000	4,600	NT	0.36

*Right postganglionic cardioaccelerator nerve in cats.

†No emesis at 800 μg/kg.

TABLE 2

5,8-DIMETHOXY DERIVATIVES OF AMINOTETRALINS



Derivative	R′	R″	Calf Caudate *in vitro* binding IC_{50}-nM Spiroperidol	ADTN	Rotation in rats	Emesis in Dogs Induced	Antag. APO induced ID_{50}-μM/kg
5,8-ADT	H	H	14,900	13,100	—	No	4.14†
DR-31	H	CH_3	18,000	144,000	2.0*	No	0.54†
DR-71	CH_3	CH_3	15,000	69,000	2.0*	No	0.71†
JMC-193	C_2H_5	C_2H_5	NT	NT	—	NT	NT
JMB-131	H	*n*-C_3H_7	18,200	125,000	4.0*	Weak	
JMC-181	*n*-C_3H_7	*n*-C_3H_7	12,200	40,000	2.0*	NT	NT

*No rotation at these doses in mg/kg.

†Compounds were administered subcutaneously 20 min prior to subcutaneous apomorphine (100 μg/kg).

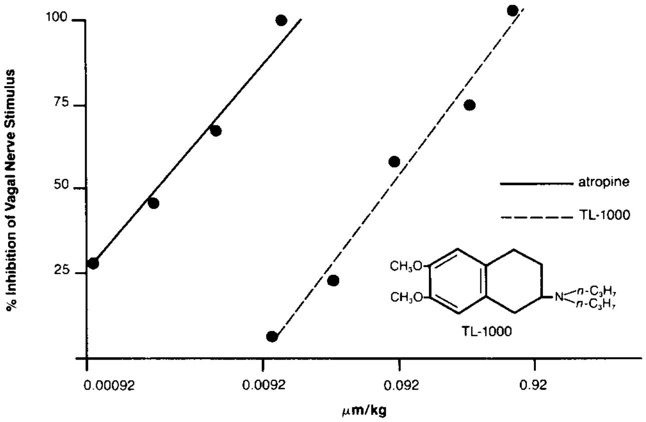
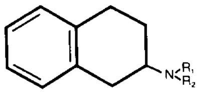


FIG. 5. Ability of atropine and (TL-1000) to inhibit depressor responses induced by stimulation of the right vagus nerve. Five dogs were used to construct each dose-response curve. The cardiac and arterial pressure responses of acetylcholine administered intravenously were not altered.

TABLE 3

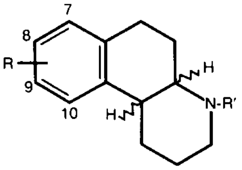
INHIBITION OF REFLEX-INDUCED PRESSOR RESPONSES BY UNSUBSTITUTED AMINOTETRALIN DERIVATIVES



		ED_{50} μmol/kg (95% Cl)	
R_1	R_2	Inhibition of Pressor Response Produced by Bilateral Carotid Occlusion—Dogs	Inhibition of Pressor Response Produced by Central Sciatic Nerve Stimulation—Cats
H	C_2H_5	0.52 (0.28– 1.1)	2.3 (1.5 –5.2)
H	n-C_3H_7	3.38 (1.3 –14.2)	0.9 (0.4 –1.4)
CH_3	CH_3	Inactive	0.16 (0.07–0.9)
C_2H_5	C_2H_5	NT	0.35 (0.12–0.65)
n-C_3H_7	n-C_3H_7	0.22 (0.15–0.33)	0.09 (0.03–0.20)
n-C_4H_9	n-C_4H_9	Inactive	Inactive

TABLE 4

DERIVATIVES OF BENZOHYDRO [F] QUINOLINES

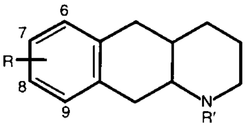


Derivative	R=*Di*-OH	Ring Juncture	R'	Cat CAN ID_{50} μM/kg	Rat Rotation APO=1	Dog Emesis APO=1
TL-224	7,8	cis	H	0.027	10*	0.024
TL-137	7,8	trans	H	0.0007	0.04	4.5
GJH171	7,8	cis	CH_3	0.62	1*	0.02
GJH166	7,8	trans	CH_3	0.0052	0.32	6.1
TL-110	7,8	cis	C_2H_5	↑HR	0.007	0.053
TL-121	7,8	trans	C_2H_5	0.00047	0.25	4.9
TL-98	7,8	cis	n-C_3H_7	↑HR	0.008	1*
TL-140	7,8	trans	n-C_3H_7	0.00027	0.27	2.7
TL-309	8,9	cis	H	↑HR	1*	0.5*
TL-305	8,9	trans	H	↑HR	1*	0.5*
TL-310	8,9	cis	CH_3	0.31		0.5*
TL-306	8,9	trans	CH_3	0.0055	0.02	0.26
TL-311	8,9	cis	C_2H_5	0.45		0.5*
TL-307	8,9	trans	C_2H_5	0.0009		2.25

*No significant activity shown at specified dose, mg/kg.

TABLE 5

DERIVATIVES OF *TRANS* BENZHYDRO [G] QUINOLINES

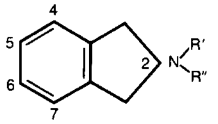


Derivative	R=*di*-OH	R′	Cat CAN* ID_{50} $\mu M/kg$	Calf Caudate *in vitro* binding IC_{50}-nM Spiroperidol	ADTN	Rat Rotation Turns per Hour/mg/kg	Dog Emesis APO=1
TL-331	6,7-*di*-OH	H	↑HR	107,000	—	8/1	0.047
TL-332	6,7	CH_3	0.0094	19,950	—	43/0.25	0.9
TL-333	6,7	C_2H_5	0.00023	99,000	2,430	35/0.25	14.0
TL-334	6,7	n-C_3H_7	0.00032	28,200		74/0.25	72.0
TL-301	7,8-*di*-OH	H	>3.0	—		7.3/1	NT
TL-302	7,8	CH_3	>3.0	—		7.0/1	NT
TL-303	7,8	C_2H_5	>3.0	—		4.3/1	1†
TL-304	7,8	n-C_3H_7	>3.0	—		40/1	0.25†

*Right postganglionic cardioaccelerator nerve in cats.
†No significant activity shown at specified dose, mg/kg.

TABLE 6

BIOLOGICAL ACTIVITY OF NON-PHENYL RING SUBSTITUTED INDANES



					Rat			
Derivative	R′	R″	Calf Caudate *in vitro* binding IC_{50}-nM Spiroperidol	ADTN	Caudate DOPA* mean Percent Reduction at 4 mg/kg	Rotation turns/hr at 10 mg/kg	Dog Emesis APO=1	Mouse Activity Mean Percent Reduction at 10 mg/kg
49-26	H	H	440,000	1,200,000	32†	Inactive	—	76†
68-11	H	CH_3	120,000	296,000	13	Inactive	Inactive	80†
66-7	CH_3	CH_3	97,000	88,000	3	—	—	—
70-22	H	C_2H_5	230,000	474,000	—	Inactive	—	74†
64-11	C_2H_5	C_2H_5	88,000	182,000	—	304	0.032	51†
71-13	H	n-C_3H_7	200,000	297,000	0	Inactive	—	22
60-36	n-C_3H_7	n-C_3H_7	49,000	15,600	71†	289	0.039	64†

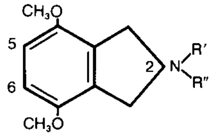
*Control DOPA in caudate nucleus=3.78 ± 0.26 ng/mg tissue.
†The value is significantly different from saline control, $p<0.05$.

transmission in the dog without muscarinic receptor involvement (Fig. 5). Similar inhibitory responses were found using isolated cat atria in which postganglionic cholinergic nerve terminals can be activated with field stimulation. The compound produces no inhibition of adrenergic transmission. Possible involvement of cholinergic transmission within the CNS has not been evaluated.

Simple chemical structures are capable of exhibiting dopamine receptor agonist properties involving primarily the central nervous system. The most active derivative is the N-*di*-*n*-C_3H_7 derivative (TL-68). This agent induces gnawing in rats at a dose of 1 mg/kg (postsynaptic). Another apparent action involving the CNS is the marked ability of this compound and structural analogs to inhibit reflex activation of the adrenergic nervous system in both cats and dogs. See Table 3 for the effective dose for 50% of the group (ED_{50})

TABLE 7

BIOLOGICAL ACTIVITY OF 4,7-DIMETHOXY INDANE DERIVATIVES



Derivative	R′	R″	Calf Caudate *in vitro* Binding IC_{50}-nM		Rat		Dog Emesis Potency Ratio to APO=1	Mouse Reduction in Activity ID_{50} (μM/kg)
			Spiroperidol	ADTN	Caudate DOPA* mean Percent Reduction at 4.0 mg/kg	Rotation Potency Ratio to APO=1		
15	H	H	252,000	851,000	6.0	8.7‡	—	20.7‡
31	H	CH_3	80,300	130,000	32†	8.2‡	—	5.95
17	CH_3	CH_3	52,000	87,500	—	0.019 (Estimated)	—	0.78
27	H	n-C_3H_7	111,000	980,000	81†	7.4‡	—	5.2
127	n-C_3H_7	n-C_3H_7	8,600	4,000	68.0†	0.13	0.13	4.1

*Control DOPA in caudate nucleus=3.78 ± 0.26 ng/mg tissue.
†The value is significantly different from saline control, $p < 0.05$.
‡No significant activity shown at the specified dose, μmol/kg.

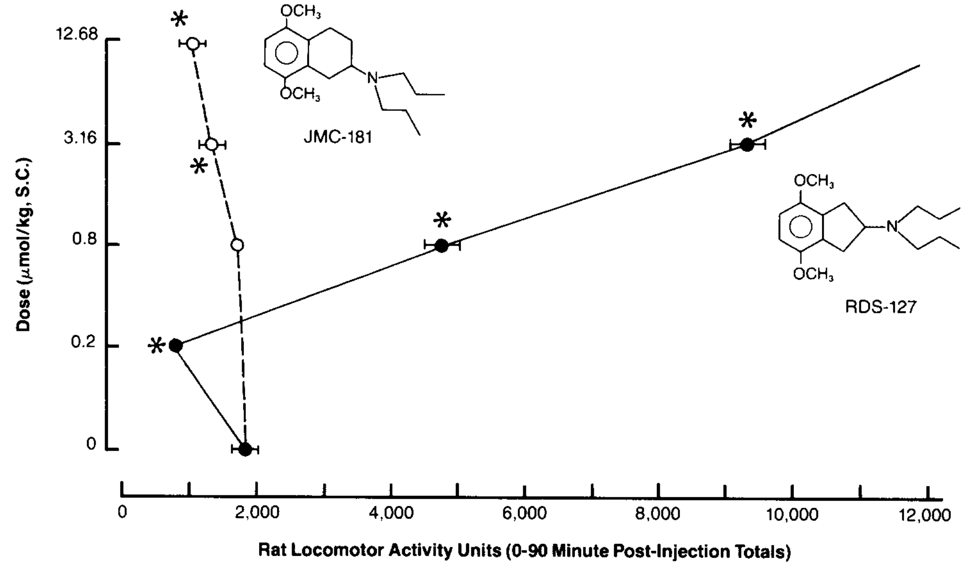


FIG. 6. Dose-response curves showing inhibition of locomotor activity in rats at low doses and induction of hyperactivity by the *bis* methoxy indane derivative (RDS-127). The aminotetralin analog (JMC-181) was only a weak inhibitor of locomotor activity.

values. The duration of action is greater than one hour. Inhibition of vasopressor reflexes is accompanied by hypotensive action (maximum: 20 mm Hg) and bradycardia (maximum: 15 beats/min). Use of various receptor antagonists indicates that the mechanism may involve other than α_2- or dopamine receptors. TL-68 is sedative and is approximately as active as morphine in its ability to increase the reaction time of mice using the hot-plate technique.

3. Derivatives of Benzhydro [f] quinolines

Dihydroxy derivatives corresponding to either the α- or β-conformer of dopamine are very active presynaptic inhibitors (see Table 4). Maximal dopamine receptor agonist activity is found with the *trans* isomers. Tertiary amine substitution is required, and little difference in activity is found for N-methyl, -ethyl or -propyl substitution.

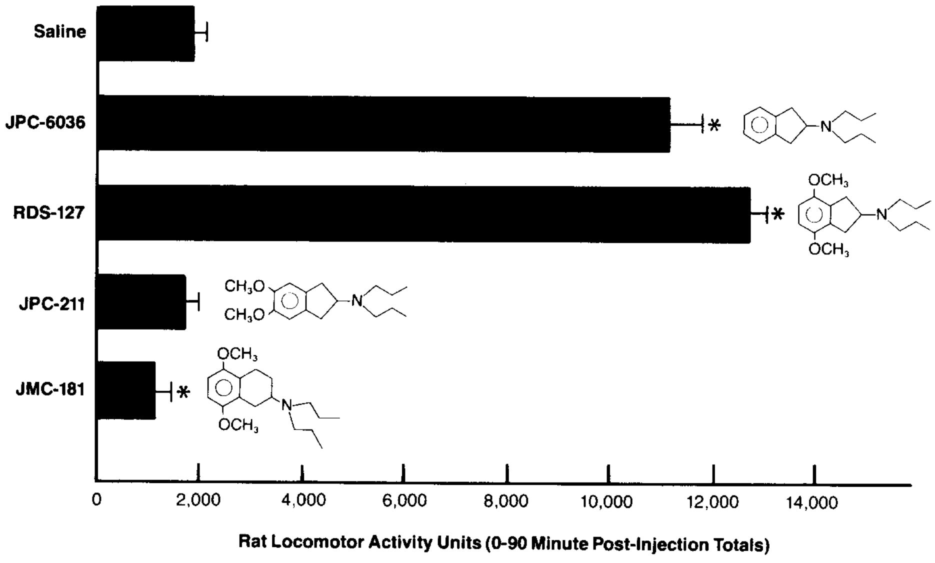


FIG. 7. Ability of indane and aminotetralin analogs to alter locomotor activity in rats. Note the importance of positional isomers of methoxy derivatives (RDS-127 vs JPC-211). All compounds were administered subcutaneously at 12 μM/kg.

4. *Derivatives of Benzhydro [g] quinolines*

Activity is summarized in Table 5. Compounds corresponding to the α-conformer of dopamine are perhaps the most potent presynaptic dopamine receptor agonists yet described. The ED_{50} of TL-333 to inhibit sympathetic neuronal transmission in the cat is 0.1 μg/kg. Compounds corresponding to the β-conformer of dopamine (spatially similar to isoapomorphine) are several hundred-fold less active than their α-conformer analog. TL-333 binds preferentially to ADTN binding sites, which probably indicates binding to presynaptic receptors.

5. *Unsubstituted Indane Derivatives*

The biological activity of these simple chemical structures is summarized in Table 6. The primary amine is a long-acting sedative in mice. The N-*di*-alkyl derivatives demonstrate weak dopamine receptor agonist activity. The affinity for both pre- (ADTN binding) and post- (spiroperidol binding) synaptic receptor binding sites increases as the N-alkyl side chain increases in length.

6. *Methoxy Derivatives of Indane*

The biological activity of these derivatives is shown in Table 7. Binding and bioassay tests indicate that tertiary amines are necessary for noticeable interactions with dopamine receptors. Maximal activity in this and other series is found with N-*di*-C_2H_5 and N-*di*-*n*-C_3H_7 derivatives.

One agent (RDS-127) was found to exhibit potent dopamine receptor agonist properties as well as several unexpected behavioral changes. Some of these properties are summarized as follows:

a. Peripheral adrenergic nervous system. The ED_{50} to inhibit adrenergic transmission is the same found for apomorphine, 20 μg/kg. The inhibition is readily reversed by haloperidol.

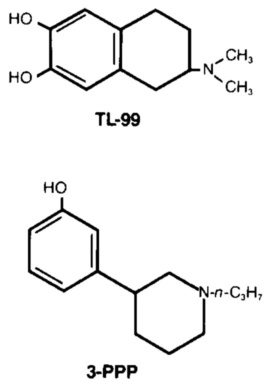


FIG. 8. Structures of two compounds that have been reported to be more selective for presynaptic than postsynaptic sites in the striatum.

b. Central nervous system. Rat locomotor activity is altered in a biphasic manner with RDS-127. These responses are shown in Fig. 6. Low doses, 64 μg/kg, inhibit locomotion and doses above 200 μg/kg produce a lengthy increase in locomotion (>5 hr). Also shown in Fig. 6 is the failure of the aminotetralin analog to increase locomotor activity. It did exhibit weak activity as an inhibitor of locomotion. Figure 7 illustrates that the non-methoxy analog of RDS-127 exhibits the same potency as RDS-127 when locomotor activity is compared. Note that a sharp reduction in activity was found for the 5,6-*di*-methoxy indane analog. RDS-127 is approximately equal in activity to apomorphine when evaluated for ability to inhibit dopa synthesis in either the nigrostriatal pathway or mesolimbic system. N-*di*-alkyl substitutions, particularly C_3H_7 (RDS-127), markedly increase the affinity for both spiroperidol and ADTN binding sites.

Compounds thus far evaluated indicate that dopamine receptors are not homogeneous. Two compounds that show selectivity for presynaptic receptors are shown in Fig. 8. 3-PPP [10] appears to be more selective than TL-99 [17]. Dopamine receptor agonists probably also vary in their ability to interact with postsynaptic sites. Likewise, variations in ability to modify function of other neurotransmitters within the CNS will probably be described in the future.

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